UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,559	03/07/2002	Yasushi Ochiai	4367-0101P	9100

2292 7590 01/25/2006

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,559	OCHIAI ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,9,10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,9,10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 C.F.R. §1.114, the Request for Reconsideration under 37 C.F.R. §1.111 and Applicant's Arguments/Remarks, all filed 11/02/05 is acknowledged. Examiner also acknowledges Applicant's request for personal interview.

Claims 1, 3, 5-7, 9, 10 and 12-14 are pending in this action. Claims 2, 4, 8 and 11 have previously been cancelled. Claims 1, 3, 5-7, 9, 10 and 12-14 are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/02/05 has been entered.

Inventorship

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5-7, 9, 10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pierre *et al.* (US Pat. No. 5,300,318).

Pierre *et al.* teach granulates of alimentary and/or medicinal active principles intended for feeding or treating ruminants are polished by spraying a solution of one or more active

principles, resins and/or sugars onto the said active principles. The polished active principles are then coated with a polymer providing protection in the rumen (see Abstract). It is preferred to employ an aqueous solution of active principle and especially a solution sprayed onto a lysine and/or methionine granulate. The base granulate which is subjected to the polishing operation may be made from lysine hydrochloride crystals (col. 1, lines 55-61). The active principle is generally an amino acid such as methionine, lysine or one of its salts, phenylalanine, histidine, arginine, or tyrosine, a medicament such as a vitamin, antibiotic, or antiparasitic agent, or a protein. The preferred active principle is lysine, in which case a homogeneous granulate is obtained, consisting of a lysine core polished with a lysine film (col. 1, line 66 – col. 2, line 9). The granulate is screened so as to retain a granulate distribution between 200 and 4000 μm (col. 2, lines 15-17).

According to Pierre *et al.*, the coating contains at least one component, which is chosen from basic polymers, copolymers or mixtures. The coating mixture solution is sprayed onto the polished granulate using a fluidized bed or any other spraying apparatus (col. 2, line 61 – col. 3, line 20). The granulate obtained after coating exhibits improved stability (col. 3, lines 30-34). Pierre *et al.* are silent regarding the granular strength.

It is the Examiner's position that Applicants have not demonstrated any unexpected or surprising results, which accrue from the claimed granular strength range, since the prior art clearly teaches a similar process of granulation whereby drug granules are sprayed with a solution of a water soluble drug on a crystal of said water soluble drug and a further coating with a release control film coating agent is applied to the drug granule. The art also teaches obtaining granules that exhibit improved stability over past formulations. No significant distinction is

observed between the instant invention and the prior art, since the prior art initially teaches an effective method for the process of forming coated drug granules, whereby the granules provide for enhanced stability, as similarly desired by the Applicant. Furthermore, one of ordinary skill in the art would be fully capable of determining suitable and effective granular strength ranges through the use of routine or manipulative experimentation, to obtain the best possible results, as these are indeed variable parameters established within the art.

Claims 1, 3, 5-7, 9, 10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koyama *et al.* (US Pat. No. 5,855,914).

Koyama *et al.* teach granules and methods for producing granules having a core and having an increased granule strength, that are produced by spraying core granules with a dispersion of a low substituted hydroxypropylcellulose (L-HPC), and if necessary, simultaneously applying a dusting powder. The granules having a core thus obtained exhibit increased granule strength and improved disintegrating property. An active ingredient, such as drug can be contained in the dispersion, dusting powder or core granules (see Abstract).

The core granules include, for example, spherical granules, based on non-pareil seeds and the core granules in themselves may be a different active ingredient other than the active ingredient contained in the dispersion or dusting powder. The core granules may be coated with waxes or polymers to produce the cores. The dispersion may additionally have the active ingredient and other additives other than the L-HPC uniformly dispersed and/or dissolved therein (col. 2, lines 30-45). The active ingredients in the form of granules are listed at column 2, lines

46 – col. 3, line 7 and include, for example, drugs for the central nervous system, respiratory organs, digestive organs, etc.

According to Koyama *et al.*, granulation is carried out, while nucleus granules are sprayed with a dispersion and/or solution of L-HPC and the active ingredient and/or additives, if necessary, and are applied with a dusting agent. The granules obtained have a core with uniform particle size (col. 3, line 57 – col. 3, line 4).

The granules are subjected to further coating to provide for flavor-masking coating, enteric coating, gastric coating or sustained-release coating, etc. and may be coated midway during the production for the purpose of stabilization, when the active ingredient is properly formulated. The granules may be filled into capsules or mixed with other components to produce tablets (col. 4, lines 5-13).

Coating agents include, for example, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, ethylcellulose, Tween 80 and the like (col. 4, lines 14-23). The granules having a core as obtained by these methods show increased granule strength and improved disintegration property (col. 4, lines 24-26).

The Examples at columns 4-8 demonstrate the production of uniformly coated granules having cores that were free from granule breakage during the coating process in each instance.

While Koyama *et al.* do not teach the instant granular strength (650-2500 gf/mm^2), the Examiner points out that, generally differences in granular strength will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such granular strength is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the Applicant's have not demonstrated any unexpected results in the granular strength range claimed. The prior art explicitly teaches processes for forming granules wherein active ingredients are sprayed onto granule cores and also teaches the further subjection of coating on the granules. Even further, the prior art clearly teaches stabilized granules that exhibit increased granular strength and teaches granule cores that are free from granule breakage during the coating process, which is a similar objective desired by Applicant. Therefore, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 11/02/05 have been fully considered but they are not persuasive.

Firstly, Applicant argued regarding the 35 U.S.C. 103(a) rejection of claims 1, 3, 5-7, 9, 10 and 12-14 over Pierre *et al.* (US '318) stating, "Pierre et al. does not provide any suggestion regarding granular strength and/or tabletting of coated granules. In contrast, the instant invention provides granules having sufficient strength, capable of maintaining a coating film during tabletting processes and thereby also allow for the manufacture of tablets from the coated granules having desirable and suitable dissolution characteristics. The method of claim 1 is also distinguished from Pierre et al, since a 'rotary fluidized bed granulate coating apparatus is used by the present inventors, which is different from the granulator of Pierre et al. The instant

invention recites the use of a rotary fluidized bed granulator, Pierre et al. use a Uniglatt apparatus (which is a non-rotary fluidized bed coating device). No teaching in Pierre et al. is cited that would lead to unexpected results, being a difference in resistance ability to acid solution. No information on granular strength and/or properties of coated granules are cited in Pierre et al."

These arguments have been considered, but were not found persuasive. Pierre et al. teach a process of granulation whereby drug granules are sprayed with a solution of a water-soluble drug on a crystal of said water-soluble drug and a further coating with a release control film-coating agent is applied to the drug granule. The art recognizes obtaining granules that exhibit *improved stability* over past formulations, of which, Examiner notes, the instant invention also desires an objective of achieving improved stability. Admittedly, while Pierre et al. are silent with respect to the particular granular strength, Applicant's have not demonstrated that a patentable distinction arises from the claimed granular strength, nor have Applicants demonstrated that the granules produced by Pierre et al's process would not have sufficient or ample strength to be suitable for further coating procedures. Pierre et al. teach a similar process to coat their drug granules, as desired by the instant invention. Furthermore, the Examiner notes that one skilled in the art through routine or manipulative experimentation can readily determine suitable or effective granulation strengths, as these are variable parameters attainable within the art. Regarding the particular 'rotary fluidized bed coating apparatus', no patentable distinction is observed through Applicant's use of the rotary apparatus since such coating apparatuses are routinely employed in the art to obtain suitable particles, granules and the likes thereof. Moreover, Pierre *et al.* teach at column 3, lines 18-20 that 'the coating mixture is sprayed using a fluidized bed *or any other spraying apparatus'*. Although Uniglatt is the preferred apparatus, the

Examples of Pierre *et al.* are not limiting to the possible coating apparatuses that can be employed in the formulations of Pierre et al. With regard to Applicant's arguments that 'Pierre do not teach unexpected results of a difference in resistance ability to acid solution, as is achieved with the present invention', Applicant's arguments were not persuasive. Applicant's argument of 'unexpected results achieved by a difference in resistance ability to acid solution' is a limitation not recited in the claims nor interpreted into the claims. A method for producing granules is being claimed, of which the prior art teaches an effective method for producing coated drug granules. Moreover, it appears that the issue would be a difference of degree only, which is not seen as a patentable distinction. Examiner notes, that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argued regarding the 35 U.S.C. 103(a) rejection of claims 1, 3, 5-7, 9, 10 and 12-14 over Koyama et al. (US '914) stating, "As also evidenced in the previously submitted Third declaration of Mr. Ochiai (filed 06/06/2005), test results provided show that the granular strength of the present inventive granules is quite distinct and different from that of Koyama et al. The granules of the prior art do not have enough strength for tabletting without substantial amount of binder."

Applicant's arguments have been considered, but were not persuasive. Admittedly, while Koyama *et al.* do not teach the instant granular strength (650-2500 gf/mm^2), Koyama et al. do clearly teach and recognize obtaining stabilized granules that exhibit increased granular strength and they Koyama et al. teach granule cores that are *free from granule breakage* during the coating process. Thus, the Koyama et al. reference is drawn to stabilized granules having

sufficient granular strength, as also desired by Applicant. The prior art explicitly teaches processes for forming granules wherein active ingredients are sprayed onto granule cores and also teaches the further subjection of coating on the granules.

With regards to Applicant's arguments regarding the Ochiai Declarations (3 in total) submitted by Applicant, the Declarations have been carefully considered, but were not found persuasive. The declaration filed 06/06/05 is not commensurate in scope with the claims. The declaration presents comparison data using Riboflavin granules, however there are no claims directed to the use of Riboflavin. Moreover, while Applicants claim 'the absence of a binder', the Declaration states at page 10, lines 1-3 that '*certain amount of binder* (such as PVP -Povidone) *is necessary to have granular strength* of around 650 g/mm2. Therefore, Applicant's statement that 'certain amount of binder is necessary to have granular strength' is contradictory in nature to the claim recitation 'the absence of binder'. Furthermore, the prior art explicitly teaches and recognizes the use of polyvinylpyrrolidone (povidone) to provide for increased strength of granules (see for instance, Koyama et al. '914, column 1, lines 64-66). It is the position of the Examiner that no unexpected results have been established in the granular strength claimed by Applicants since the prior art addresses the concerns and objectives of achieving increased granular strength with improved stability.

There is no significant distinction observed between the instant invention and that of the cited art since the art clearly teaches processes for producing coated drug granules, comprising sprayed solutions of water-soluble drugs onto said drugs. Suitable coating techniques are also disclosed in the art to provide for stabilized coated drug granules. The prior art teaches granules having increased strength whereby the granules are free from breakage during coating processes.

Thus, for the above-delineated reasons, the instant invention is rendered *prima facie* obvious and unpatentable over the cited art of record.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

H. N. Sheikh 

Patent Examiner

Art Unit 1615

January 23, 2006